

REMARKS***Status of the Claims***

Claims 17, 21-24, 26, 28, 29, 31, 33, 38, and 41-44 are in the application.

Claims 17, 21-24, 26, 28, 29, 31, 33, 38, and 41-44 have been rejected.

Claims 17, 24, 28, and 29 have been amended.

Upon entry of this amendment, claims 17, 21-24, 26, 28, 29, 31, 33, 38, and 41-44 will be pending.

Summary of the Amendment

Claims 17 and 24 have been amended to recite particular embodiments of the invention more precisely. Support for the amendment appears throughout the specification and claims as originally filed.

Claim 28 has been amended to recite the elements of canceled claim 27. Support for the amendment appear throughout the specification and claims as originally filed.

Claim 29 has been amended to correct its dependency. Support for the amendment appear throughout the specification and claims as originally filed.

No new matter has been added.

Claim Rejection Under 35 U.S.C. §112, second paragraph

Claims 17, 21-24, 26, 28, 29, 31, 33, 38, 41-44 stand rejected under 35 U.S.C. §112, second paragraph for allegedly being indefinite. Claim 17 has been amended to remove the terms “functional fragment thereof.” The amendment obviates the basis of the rejection.

Applicants respectfully request that the instant rejection be withdrawn.

Claim Rejection under Section 102(b)

Claims 17, 21, 31, 33, 38 and 42 stand rejected under section 102(b) over the Alila reference. Applicants respectfully traverse.

“A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference.” *Verdegaal Bros. v. Union Oil Co. of California*, 2 USPQ 2d 1051, 1053 (Fed. Cir. 1987). See MPEP § 2131. The standard for showing an inherent disclosure in the prior art is suggested in MPEP § 2112, “To establish inherency, the extrinsic evidence **‘must make clear that the missing descriptive matter is necessarily present** in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.”” (emphasis added). The Patent Office has failed to meet such a standard for establishing an inherent disclosure in the Alila reference.

The claimed invention is directed to methods of “stimulating angiogenesis in a subject who as a muscle injury.” The Alila reference fails to disclose a method to stimulate angiogenesis. This is clear because the Alila reference fails to disclose a subject with a muscle injury and fails to suggest stimulating angiogenesis, or the growth of new blood vessels. Assuming arguendo, Alila describes a “muscle injury,” a method to stimulate angiogenesis in such a subject by administration of a nucleic acid construct encoding IGF-I is not necessarily present in Alila. Instead, Alila discloses the effects of IGF-I on **neurons** when expressed in muscle tissue.

Alila does disclose the induction of GAP-43, a nerve-specific growth associated protein that, by its own admission, “is an indicator of motor neuron sprouting.” (page 1794, col. 1, paragraph 2). However, it is clear that neuron sprouting is not angiogenesis. In addition, the Patent Office further mischaracterizes myoneuropathies being “muscle injury.” Neuron damage is not muscle injury. Alila fails to teach or suggest a subject with muscle injury, much less a method to stimulate angiogenesis in a subject with a muscle injury.

Moreover, Alila does not teach or suggest that genetic material encoding IGF-I when administered to a subject necessarily leads to stimulating angiogenesis. The Alila reference only states that “Gene therapy using formulated plasmids **may have potential utility** in the treatment of local myoneuropathies by increasing tissue concentration of **hIGF-I or other growth factors** in the affected muscles without systemic effects.” (emphasis added). The

reference fails to teach treatment of muscle injury, and moreover, the stimulation of angiogenesis necessarily results. Thus, Alila fails to disclose each and every element of the claims.

Alila does not anticipate the claims. Applicants respectfully request that the rejection of claims 17, 21, 31, 33, 38, and 42 under 35 U.S.C. § 102(b) should be withdrawn .

Claim Rejection under Section 103

Claims 22 and 23 have been rejected under 35 U.S.C. 103(a) as unpatentable over Alil, *et. al.*, in view of van Deuterkom, *et. al.* (hereinafter “Deuterkom”). Applicants respectfully traverse.

Applicants maintain that the teachings of Alil and Deuterkom cannot be combined to arrive at the claimed invention because the combination fails to teach the claimed invention. In addition, Applicants assert that one of ordinary skill in the art would not combine the teachings of the claimed invention because one of ordinary skill in the art would not recognize the benefit of the combination of references.

Alil is discussed above, and the same arguments are applied here.

It is asserted that it would have been obvious for one of ordinary skill in the art to modify the method of Alil to mix the isolated nucleic acid expression construct with a transfection – facilitation system, such a liposome with a reasonable chance of success. (Office Action, page 7). A statement that modifications of the prior art would have been “well within the ordinary skill of the art a the time the invention was made because the references teach that all aspects of the claims were individually known in the art is not sufficient to establish a *prima facie* case of obviousness without some objective reason to combine the references. *Ex parte Levingood*, 28 USPQ 2d 1300 (BPAI, 1993). The Office has failed to provide an objective reason to combine the references.

Deuterkom discloses methods of improving transduction of viral vectors. However, Deuterkom does not teach, mention or suggest methods of stimulating angiogenesis. In addition, Deuterkom does not teach a subject with a muscle injury as required by the claims. Without impermissible hindsight, one of ordinary skill would not be motivated to combine these references.

The Patent Office on Page 6 of the Office Action improperly supports the obviousness rejection when stating the rule of same chemical products having same properties. The “stimulating angiogenesis” function is not a “property” of the claimed nucleic acid sequence encoding IGF-1, but instead it is a downstream physiological response to the expressed IGF-1 in muscle. Simply knowing or having IGF-1 does not necessarily result in “stimulating angiogenesis.”

Neither Alil nor Deuterkom reference teaches or suggests stimulating angiogenesis, or stimulating angiogenesis in a subject with a muscle injury. One of ordinary skill in the art would not be motivated to modify a reference disclosing nerve regeneration with a reference disclosing liposomes to arrive at a method of stimulating angiogenesis using the claimed nucleic acid construct in combination with a transfection-facilitating system before delivering the isolated nucleic acid expression construct into the muscle tissue of the injured muscle of the subject. The Office has therefore not established a *prima facie* case of obviousness.

The Office has failed to properly establish a *prima facie* case of obviousness under 35 U.S.C. §103(a). Applicants respectfully request that the rejection be withdrawn.

Claims 17, 24, 28, 29, 41, 43, and 44 stand rejected under 35 U.S.C. § 103(a) over Alila in view of Draghia-Akli, Fewell, and Isner. Applicants respectfully traverse.

Applicants maintain that the teachings of Alil, Draghia-Akli, Fewell, and Isner cannot be combined to arrive at the claimed invention because the combination of the teachings does not yield the claimed invention. Applicants assert that one of ordinary skill in the art would not combine the teachings because one of ordinary skill in the art would not recognize the benefit of the combination of references.

Again, applying the arguments of the above-section directed to the 102 and 103 rejections, the Alila reference fails to disclose the claimed invention directed towards methods of stimulating angiogenesis with the provided nucleic acid expression constructs. Alila fails to disclose administration of nucleic acid constructs with muscle injury. The secondary references

cited herein fail to make up for the deficiencies of the Alila reference. As a result, these cited references, alone or in combination, fail to render the claimed invention obvious.

Accordingly, it is respectfully requested that this rejection be withdrawn.

Conclusion

Applicants respectfully submit that, in light of the foregoing comments and amendments, all pending claims are now in condition for allowance. A Notice of Allowance is therefore requested.

The Commissioner is hereby authorized to charge any deficiencies of fees and credit of any overpayments to Deposit Account No. 50-0436. If the Examiner has any other matters which pertain to this Application, the Examiner is encouraged to contact the undersigned to resolve these matters by Examiner's Amendment where possible.

Respectfully Submitted,

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